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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,699	08/05/2003	Pablo Umana	1975.0010004/TJS	5489

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
02/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,699	UMANA ET AL.	
	Examiner	Art Unit	
	MICHAEL BURKHART	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/14/2008; 11/10/2008; 1/27/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *143-158 and 161-171* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *143-158, 161-171* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/14/08;7/2/08;9/10/08* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 11/10/2008 and 1/27/2009 has been entered. Claims 143-158 and 161-171 are pending and under examination.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 121 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/294,584, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. See the 35 USC 112 1st ¶ rejection (New Matter)

below. The instant claims are given a priority date of 8/5/2003, the filing date of the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 143-158 and 161-171 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons made of record in the Office Actions dated 10/31/2006, 11/15/2007 and for reasons set forth below. This is a New Matter rejection.**

Applicants claim recombinant antibodies having increased Fc-mediated cellular cytotoxicity (ADCC) or increased Fc receptor binding affinity wherein said antibodies have an increased proportion of nonfucosylated oligosaccharides (all of the pending claims) relative to a corresponding antibody that has not been glycoengineered. The first disclosure of such broad limitations was in claims 106 and 107 (now canceled) of the preliminary amendment of 12/22/2004. No such limitations are found in the claims as originally filed in this application (10/633,699, claims 1-85, filed 8/5/2003). There is no support for such broad limitations, or evidence that applicants considered such limitations as a part of their invention, in the parent

application, 09/294,584 (now U.S. patent 6,602,084), thus the instant claims comprise New Matter. Rather, applicants' disclosure repeatedly indicates that antibodies engineered to have an increased proportion of complex N-linked oligosaccharides with bisecting GlcNAc (e.g. column 6, lines 26-28 and lines 46-53, column 7, lines 14-26 and column 16, lines 55-61 of the '084 patent) are the invention. Non-fucosylated oligosaccharides are only mentioned once, in reference to a single example of a specific antibody produced in modified CHO cells, (i.e. the CE7-15t, -30t, and -60t preparations from Example 3, column 26 of the '084 patent) and are not disclosed as correlated with an increase in ADCC for this antibody, or for antibodies in general. Rather, the increase in ADCC for the CE7 antibodies was correlated with an increase in bisected complex oligosaccharides (column 27, lines 9-13), not a decrease in fucosylated oligosaccharides. This is probably because the sample with the greatest proportion of non-fucosylated oligosaccharides, CE7-15t, did not show an increase in ADCC (see Figs. 9 and 12 of the '084 patent). The antibodies presented in the instant application that had increased ADCC did not have a "majority" of nonfucosylated oligosaccharides, nor were they completely devoid of fucosylated oligosaccharides (within the scope of the instant claims). There is no analysis or discussion of what the actual "proportion of nonfucosylated oligosaccharides" inherently found on the antibodies of the specification might be. Analysis of the oligosaccharide profiles of the CE7-60t and -30t antibodies reveals that a majority of the oligosaccharides are fucosylated. In Fig. 9C and D (CE7-60t and -30t, respectively), the peaks at m/z 1486, 1648, 1689, and 1851 all represent fucosylated oligosaccharides according to the disclosure (e.g. pages 37-39 and Figs 10-11), and, absent evidence to the contrary, represent a majority of the oligosaccharides: the m/z 1689 and 1851 are the two largest peaks in Fig. 9C and D. The m/z 1689 and 1851 peaks

represent bisected complex oligosaccharides that are fucosylated, according to Fig. 11, the very peaks which led applicants to conclude that an increase in bisected complex oligosaccharides leads to an increase in ADCC (e.g. pages 36-39 of the specification).

Regarding new claim 168, there is no disclosure, either literal or inherent, of antibodies having only up to about 50% complex oligosaccharides. In one sense, if only 50% of the glycans were complex structures, this would mean the remaining 50% of the glycans would have to be either high-mannose or hybrid glycans. There is no disclosure of such a high percentage of high mannose or hybrid glycans in the disclosed antibodies. What is disclosed is that up to 50% of the oligosaccharides may be bisected, complex glycans.

Hence, the instant claims are given a priority date of 8/5/2003, the filing date of the instant application.

Response to Arguments

Applicant's arguments filed 5/14/2008 have been fully considered but they are not persuasive. Applicants present no new arguments against this rejection in the response dated 5/14/2008.

Applicant's arguments filed 11/10/2008 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) support for the amended claims can be found in the claims as filed, page 38, and Figs. 9A-E; 2) although not directed to this rejection *per se*, applicants assert that decreased fucosylation is a necessary characteristic of the claimed antibodies because oligosaccharides first modified by the GnTIII enzyme can no longer be fucosylated by the α-1,6-fucosyltransferase, e.g. the teachings of Schachter et al.

Regarding 1), as discussed above, the original claims did not mention "an increased proportion of nonfucosylated oligosaccharides"; a search of the instant specification does not reveal the term "nonfucosylated." There is no literal support for the term "proportion of nonfucosylated oligosaccharides", thus, the specification must inherently support this broad limitation of possible antibodies and proportions of nonfucosylated oligosaccharides. It does not for reasons set forth above. Figure 9 (there are no figures 9A-E in the specification as originally filed, as applicants assert) supports the analysis above, that is, many of the antibodies comprised significant amounts (e.g. a majority) of fucosylated oligosaccharides. Applicants present no response to these facts.

Regarding 2), many of the oligosaccharides on antibodies prepared in GnTIII-expressing CHO cells are clearly fucosylated according to applicants own interpretation and figures (again, see Example 3 and Figs. 9-11). This is because fucosylation can occur before the action of GnTIII, as is clearly demonstrated in Figs. 10 and 11: that is, the substrates for the GnTIII enzyme are already fucosylated in these figures prior to the action of GnTIII. Applicants have yet to explain how then the instant application can provide support for antibodies having, for example, none or very little fucosylation (within the claimed scope) and still possess increased ADCC. It is not an inherent function of the disclosed antibodies for reasons set forth above, i.e. a negative correlation was found between increased ADCC and nonfucosylated oligosaccharides.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 147 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 147 recites that the GlcNac residues are carried "on complex, hybrid N-linked oligosaccharides." The terms "complex" and "hybrid" when applied to N-linked oligosaccharides are, as best understood, mutually exclusive. Complex, or biantennary, oligosaccharides have both "arms" of the original high mannose structure replaced with, for example, galactose or N-acetylglucosamine residues. See Figure 1 of the instant specification. Hybrid oligosaccharides have only one such "arm" replaced, with the other remaining a "high mannose" or mannose arm. Again, see Figure 1, in particular the structure termed "M_5GnGn^bG Bisected Hybrid." It is thus unclear how an oligosaccharide can be both complex and hybrid. A search of the specification reveals no use of the term "complex, hybrid." The term has been interpreted as "complex or hybrid N-linked oligosaccharides" for prior art purposes.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 143-145, 147-155, 157, 158, 161-167 and 169-171 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakamura et al (Cancer Res., 1994, cited by applicants) as

evidenced by Shinkawa et al (JBC, 2003, of record) and Raju et al (Glycobiol, 2000, cited by applicants).

Nakamura et al teach the production of the mouse/human chimeric antibodies KM 966 and KM 967 in rat myeloma YB2/0 cells (abstract and page 1513, second column, second full ¶). Mice bearing tumors were treated by administration of the antibodies (page 1514, second column, third full ¶). Raju et al teach that rat IgG's in general inherently have bisected oligosaccharides (Table III, structure nos. 32 and 33/34, as shown in Scheme 2, page 479), which are produced by the GnTIII enzyme (page 477, second column, second full ¶). Also see Fig. 4C and page 483, first column of Raju et al. Shinkawa et al confirm that the YB2/0 cell line inherently produces antibodies with bisected oligosaccharides (Fig. 2 and page 3469, first column, first ¶). Shinkawa et al further teach that the bisected oligosaccharides are due to GnTIII expression (page 3466, second column, third full ¶). As evidenced by Shinkawa et al, the YB2/0 cells express low levels of α1,6-fucosyltransferase, therefore producing antibodies having a greater proportion of nonfucosylated oligosaccharides than those produced in CHO cells. For example, YB2/0-produced antibodies had 34% and 91% nonfucosylated oligosaccharides versus 9% nonfucosylated oligosaccharides for antibodies produced in CHO cells (see entire document, in particular Fig. 2, Table I, and page 3469, first column, last ¶). Furthermore, the low levels of fucosylated oligosaccharides were linked to an increase in ADCC (see abstract Figs. 1, 3, and 4, and page 3469, second column to page 3470, first column), which was attributed to an increase in affinity for FcγRIII receptor (page 3466, second column, fourth ¶). Some of the bisecting oligosaccharides were complex (Fig. 2A and C of Shinkawa et al). The antibodies of Nakamura et al were murine/human chimeras comprising the CDRs of the murine monoclonal antibodies

(specific for G_{M2}) linked to a human constant region (¶ linking first and second columns, page 1511), which comprises either the human γ1 or κ constant regions. The γ1 or κ constant regions comprise an Fc region and are considered an IgG (see the abstract of Nakamura et al). The anti- antibodies bound to a G_{M2} ganglioside antigen found on, *inter alia*, neuroblastomas (page 1511, first column, first ¶). The anti-G_{M2} antibodies are considered therapeutic as they were used to inject mice bearing tumors (abstract). The antibodies of Nakamura et al are considered to have a glycosylation pattern as taught by Shinkawa and Raju et al, which is unusual relative to other cells lines (such as CHO cells) in the low levels of fucosylation and the presence of bisecting oligosaccharides. Thus, antibodies prepared from YB2/0 cells are considered to inherently have a glycan structure that meets the limitations of claims 161, 164-167, i.e. a glycan structure as those antibodies that might be prepared from a cell manipulated to overexpress GnTIII. Applicants are reminded that product-by-process claims are not limited by the limitations of the process steps, only the structure implied by those steps. See MPEP §2113. Increased expression of GntIII would necessarily lead to increased bisecting GlcNac and reduced fucosylation according to the prior art (e.g. Schachter et al, as presented by applicants), particularly in cells that lack an endogenous GnTIII (e.g. CHO cells, also see page 3469, second column, last ¶ of Shinkawa et al discussing the glycosylation pattern of Lec10 CHO cells and their similarity to the glycans observed for YB2/0). Improvements in ADCC for antibodies with a YB2/0 glycosylation pattern versus those with a CHO cell glycosylation pattern was at least 50-fold (i.e. greater than 80%, Fig. 1 of Shinkawa et al). Absent evidence to the contrary, the antibodies of Nakamura et al comprised a CH2 domain in the constant region, as this is where the N-linked glycosylation site lies, and the antibodies exhibited ADCC activity (Fig. 4 of Nakamura et al).

Claim 143-158, 161-167 and 169-171 are rejected under 35 U.S.C. 102(b) as being anticipated by Umana et al. (WO 99/54342, cited by applicants).

Umana et al disclose chimeric anti-neuroblastoma or anti-CD20 antibodies (chCE7, C2B8) made in CHO cells transfected with a GnTIII expression vector (see pages 9-10 and 31-43). The transfected cells express GnTIII (see pages 12, last two paragraphs to page 13, last paragraph, and pages 43-45). Antibodies produced in CHO-GnTIII cells had a glycosylation pattern with fewer fucosylated glycans and increased bisected glycans (both complex and hybrid) relative to Sp2/0 and CHO cells not expressing GnTIII. The change in glycosylation was linked to an increase in ADCC (see pages 35-39 and Figures 9-11), which was thought to be Fc-receptor mediated (page 8, first ¶, page 21, first full ¶). The chCE7 antibody, at the least, is an IgG1 (page 31, first full ¶) and had a human constant, or Fc, region (¶ linking pages 31-32). Umana et al disclose that C2B8 is used in humans to treat Non-Hodgkin's lymphoma (a B cell lymphoma, wherein said term would encompass any form of Non-Hodgkin's lymphoma) and thus is considered a therapeutic antibody (see page 40, first paragraph). The increase in ADCC was at least 80% (Figure 12, page 38, second full ¶) relative to antibodies from cells not expressing GntIII. Absent evidence to the contrary, the antibodies of Umana et al comprised a CH2 domain in the constant region, as this is where the N-linked glycosylation site lies, and the antibodies exhibited ADCC activity.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 143-147, 149-155, 157, 158, 161, 162, , 164-167, and 169-171 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 246-269, 283 and 284 of copending Application No. 11/348,526. Although the conflicting claims are not identical, they are not patentably distinct from each other because the species of anti-EGFR antibody recited in the '526 claims anticipates, and thus renders obvious, the instant antibodies. EGFR is disclosed as inherently being expressed in several types of cancers (page 2 of the '526 specification).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHAEL BURKHART whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhart/
Primary Examiner, Art Unit 1633